Environmental Health Perspectives
Vol. 53, pp. 49–56, 1983

Critical Review of Epidemiologic Studies Related to Ingested Asbestos

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Thirteen epidemiologic studies of ingested asbestos conducted in five areas of the United States and Canada were reviewed and evaluated for the definitiveness and applicability regarding the development of ambient water quality standards. One or more studies found male or female associations between asbestos in water supplies and cancer mortality (or incidence) due to neoplasms of the esophagus, stomach, small intestine, colon, rectum, gallbladder, pancreas, peritoneum, lungs, pleura, prostate, kidneys, brain, and thyroid, and also due to leukemia. Several methodologic weaknesses and limitations were found in each study, leading to the determination that no individual study or aggregation of studies exist that would establish risk levels from ingested asbestos. A binomial probability analysis of the eight independent studies suggested that, while the level of male-female agreement was generally low, the number of observed positive associations in males and females for neoplasms of the esophagus, stomach, pancreas, and prostate was unlikely to have been generated by chance factors alone, and thus, may have a biological basis related to ingested asbestos. Cancers of the small intestine and leukemia were implicated to a lesser degree in this analysis. The patterns of integrated findings for most gastrointestinal cancers were somewhat consistent with patterns observed among asbestos-exposed occupational groups, whereas the patterns found for pancreatic cancer, kidney cancer, and leukemia were not consistent. It was recommended that the integrated ecologic data to date be used to generate a rough priority of specific etiologic hypotheses that should be tested in the original settings or in independent study populations using studies designed at the more definitive individual level, such as case-control studies. The Bay Area (California) and Puget Sound (Washington) were deemed to be the existing study areas most suitable for future research.

Introduction

In 1982, the U.S. Environmental Protection Agency commissioned a critical review of the major epidemiologic studies that were germane to the question of possible adverse health effects caused by ingested asbestos. Thirteen published and unpublished studies conducted in five areas of the United States and Canada were included in the review (*1–13*). This paper presents the major findings and salient points of the more detailed review found elsewhere (*14*).

Background

The genesis of all of the studies included in this review was the 1973 discovery of large amounts of amphibole asbestos fibers in Lake Superior, the source of municipal water for Duluth, Minnesota, and five small communities on the lake shore. The first epidemiologic study to appear after this discovery was conducted in Duluth by Mason et al. In 1974 (*1*). Mason's study of 1950–1969 cancer mortality rates was followed by two studies of cancer incidence rates in Duluth, the first in 1976 by Levy et al. (*2*) and the second in 1981 by Sigurdson et al. (*3*). The two Connecticut studies of Harrington et al. in 1978 (*4*) and Meigs et al. in 1980 (*5*) were prompted by the possibility of studying reliable cancer incidence data over a 35-year period through the Connecticut Tumor Registry and linking these data with information collected on asbestos-cement pipe studies done by the U.S. EPA. In Canada, the mortality studies of Wigle in 1977 (*6*) and Toft et al. in 1981 (*7*) were induced by the extent of the asbestos mining done in Quebec and by environmental surveys that revealed high concentrations of asbestos fibers in the drinking water supplies of certain cities. The

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San Francisco Bay Area cancer incidence studies of Kanarek et al. in 1980 (*8*), Conforti et al. in 1981 (*9*), and Tarter in 1981 (*10*) were motivated by the fact that several drinking water supplies come from aquifers or are stored in reservoirs that are exposed to serpentine, the parent rock form of chrysotile asbestos. The single unpublished epidemiologic study of cancer incidence conducted in Utah by Sadler et al. in 1981 (*11*) was based upon the fact that several Utah communities were known to have used predominantly asbestos-cement pipe for periods exceeding 20 years. Finally, the two studies of cancer incidence and mortality in the Puget Sound area by Severson et al. in 1979 (*12*) and Polissar et al. in 1982 (*13*) were motivated by the fact that three of the largest metropolitan areas of western Washington state have been almost constantly serviced since the early part of the 20th century by water supplies containing a wide range of chrysotile asbestos fibers.

Individual Reviews and Qualitative Integration of Findings

For each of the 13 studies, a determination was made of an overall positive, negative, or lack of association between ingested asbestos and cancer mortality or incidence. Determinations were based on general epidemiologic considerations while accounting for the strengths and weaknesses of the underlying study designs. Due to the subjectivity inherent in the assessment of research findings, the interpretations made were not always those of the authors cited.

Tables 1 and 2 show for gastrointestinal and nongastrointestinal cancer sites, respectively, a summary of results from the 13 studies. As shown here, one or more previous studies have found for males or females some association between asbestos in water supplies and cancer mortality (or incidence) for neoplasms of the esophagus (*1,8,9*), stomach (*1,2,6–9*), small intestine (*13*), colon

Table 1. Summary of studies of gastrointestinal cancer risk in relation to ingested asbestos by cancer site.[a]

Gastrointestinal cancer site, (ICD 7th revision codes)	Duluth			Connecticut		Quebec		Bay Area, CA			Utah	Puget Sound, WA	
	Mason (*1*)	Levy (*2*)	Sigurdson (*3*)	Harrington (*4*)	Meigs (*5*)	Wigle (*6*)	Toft (*7*)	Kanarek (*8*)	Conforti (*9*)	Tarter (*10*)	Sadler (*11*)	Severson (*12*)	Polissar (*13*)
All sites combined (150–159)	(+ +)	(− −)	(00)	ns	ns	(00)	(+0)	(+ +)	(+ +)	(+ +)	ns	(00)	ns
Esophagus (150)	(+ −)	(00)	(00)	ns	ns	(00)	(00)	(0+)	(+ +)	ns	ns	ns	(00)
Stomach (151)	(+ +)	(+0)	(00)	(00)	(00)	(+0)	(+0)	(+ +)	(+ +)	ns	(00)	(00)	(00)
Small intestine (152)	ns	(00)	(00)	ns	ns	ns	ns	(00)	(00)	ns	(00)	ns	(+ +)
Colon (153)	(00)	(− −)	(00)	(00)	(00)	(00)	(00)	(00)	(+0)	ns	(0−)	(− −)	(00)
Rectum (154)	(+ +)	(00)	(00)	(00)	(00)	(00)	(00)	(00)	(00)	ns	(00)	ns	(00)
Biliary passage/liver (155–156A)	(00)	(00)	(00)	ns	ns	ns	ns	(00)	(00)	ns	ns	ns	(00)
Gallbladder (155.1)	ns	(00)	(00)	ns	ns	ns	ns	(0+)	(00)	ns	(0+)	ns	(00)
Pancreas (157)	(0+)	(+ +)	(0+)	ns	(+0)	(0+)	(00)	(0+)	(+ +)	ns	(00)	ns	(00)
Peritoneum (158)	ns	(00)	(00)	ns	ns	ns	ns	(+ +)	(0+)	ns	(00)	ns	(00)

[a](Male, female) = association with ingested asbestos: + positive, 0 none, − negative, ns = not studied.

Table 2. Summary of studies of nongastrointestinal cancer risk in relation to ingested asbestos by cancer site.[a]

Nongastrointestinal cancer site (ICD 7th revision codes)	Duluth			Connecticut		Quebec		Bay Area, CA			Utah	Puget Sound, WA	
	Mason (*1*)	Levy (*2*)	Sigurdson (*3*)	Harrington (*4*)	Meigs (*5*)	Wigle (*6*)	Toft (*7*)	Kanarek (*8*)	Conforti (*9*)	Tarter (*10*)	Sadler (*11*)	Severson (*12*)	Polissar (*13*)
Buccal cavity and pharynx (140–148)	ns	ns	ns	ns	ns	(00)	(00)	ns	ns	ns	ns	ns	(00)
Bronchus, trachea, lungs (162, 163)	(+0)	ns	(00)	ns	(00)	(+0)	(+0)	(+0)	(00)	ns	ns	ns	(00)
Pleura (162.2)	ns	ns	ns	ns	ns	ns	ns	(0+)	(0+)	ns	ns	ns	ns
Prostate (177) (males only)	ns	ns	ns	ns	ns	0	0	0	+	ns	ns	ns	+
Kidneys (180)	ns	ns	ns	ns	(00)	(00)	(00)	(0+)	(00)	ns	(+0)	(00)	(00)
Bladder (181)	ns	ns	ns	ns	(00)	(00)	(00)	(00)	(00)	ns	ns	ns	(00)
Brain/CNS (193)	(00)	ns	ns	ns	ns	(00)	(00)	(00)	(00)	ns	ns	ns	(+ −)
Thyroid (194)	ns	ns	ns	ns	ns	ns	ns	(00)	(00)	ns	ns	ns	(+ +)
Leukemia, aleukemia (204)	(00)	ns	ns	ns	ns	(00)	(00)	(00)	(00)	ns	(+0)	ns	(+ −)

[a](Male, female) = association with ingested asbestos: + positive, 0 none, − negative, ns = not studied.

(*2,9,11, 12*), rectum (*1*), gallbladder (*8,11*), pancreas (*1–3,5,6,8,9*), peritoneum (*8,9*), bronchus, trachea, or lungs (*1,6–8*), pleura (*8, 9*), prostate (*9,13*), kidneys (*8,11*), brain or central nervous system (*13*), thyroid (*13*), and leukemia or aleukemia (*11,13*). The large variability in findings evident among the studies is matched by a considerable descrepancy in results for males and females within the 13 studies. Several factors might explain, at least in part, the internal and external inconsistencies in results.

First, the descrepant results may be due to differences in characteristics of asbestos exposure in the various study populations. These differences are summarized in Table 3. The relatively low number of positive associations found in Utah (*11*) and Connecticut (*4,5*) could be due to the low concentrations of asbestos in the drinking water or to the relatively short duration of community exposure in several study subareas. The virtual absence of positive findings in the most recent Duluth study (*3*) could also be due to relatively short duration of exposures as well as the amphibole fiber, which is fundamentally different from the chrysotile fibers found in the remaining study areas. By utilizing the differences in exposure characteristics, the three study areas associated with long duration of exposures (> 40 years) to chrysotile asbestos can be roughly ranked according to the concentration of fibers in their water systems. However, the resulting ranking, Bay Area (lowest), Puget Sound (intermediate), and Quebec (highest), does not appear to be related to the pattern of associations shown in Tables 1 and 2.

In addition to duration and intensity, it is also likely that other exposure factors, such as the characteristics of asbestos pipe used, the concentration of other possibly carcinogenic contaminants of water, and certain physical properties of asbestos fiber (e.g., length), vary among and within the six study areas.

As a second major factor, the different study designs employed in the various areas, coupled with the disparity in their underlying strengths and weaknesses, most likely also contributed to the observed variability in results. The most important methodologic weaknesses and limitations ascertained from the individual reviews are summarized in Table 4. The weaknesses are listed in approximate decreasing order of importance relative to their potential impact on the credibility and definitiveness of the findings.

By far the most serious limitation of all the studies conducted to date is that they are ecological or, more specifically, geographic correlation studies by design. This drawback alone does not permit a definitive conclusion to be made from any of the studies of the possible adverse health effects of ingested asbestos. The major drawback of ecological analysis for testing etiologic hypotheses is the potential for substantial bias in effect estimation. This problem, known as the "ecological fallacy," results from making a causal inference about individual phenomena on the bias of observations of groups. Theoretically, the bias resulting from ecological analysis can make an association appear stronger or weaker than it is at an individual level; however, in practice, this bias ordinarily exaggerates the magnitude of a true association, if one exists (*15–17*). Ecologic study bias can be minimized, for example, through the judicious application of ecologic regression techniques. Such techniques were employed, at least inpart, in the Connecticut study of Meigs (*5*), the three Bay Area studies (*8–10*), and the two Puget Sound studies (*12, 13*). However, the overall variability in results does not appear to be any less among or within these six studies compared to the remaining seven, which did not incorporate more refined ecologic analyses.

Much of the bias inherent in ecologic analysis results from the inability to control for confounding factors at the individual level. Table 4 shows that most of the studies reviewed did not directly control for confounding factors even at the group level. Notable exceptions are the Bay Area studies of Kanarek et al. (*8*) and Conforti et al. (*9*) and the two Puget Sound studies (*12,13*), which em-

Table 3. Characteristics of asbestos exposures in drinking water in various study populations.

Characteristic	Duluth	Connecticut	Quebec	Bay Area, CA	Utah	Puget Sound, WA
Type of asbestos	Amphibole	Chrysotile	Chrysotile	Chrysotile	Chrysotile	Chrysotile
Number of fibers/L[a,b]	1.0–30.0 – 10^6	BDL–0.7 – 10^6	1.1–1300 – 10^6	0.025–36 – 10^6	n.a.[b]	7.3–206.5 – 10^6
Population exposed	100,000	576,800	420,000	3,000,000	24,000	200,000
Maximum duration of exposure, yr	15–20	23–44	> 50	> 40	20–30	> 40

[a]BDL = below detectable limit.
[b]n.a. = data not available.

Table 4. Summary of methodologic weaknesses and limitations associated with various studies of ingested asbestos.[a]

Weakness/limitation[b]	Duluth			Connecticut		Quebec		Bay Area, CA			Utah	Puget Sound, WA		Total across studies
	Mason (*1*)	Levy (*2*)	Sigurdson (*3*)	Harrington (*4*)	Meigs (*5*)	Wigle (*6*)	Toft (*7*)	Kanarek (*8*)	Conforti (*9*)	Tarter (*10*)	Sadler (*11*)	Severson (*12*)	Polissar (*13*)	
Ecologic study design	*	*	*	*	*	*	*	*	*	*	*	*	*	13
Insufficient latency period	*	*	*	–	–	–	–	–	–	–	*	–	–	4
Death certificate data	*	–	–	–	–	*	*	–	–	–	–	–	–	3
Duration and/or intensity of exposure low	*	*	*	*	*	–	–	–	–	–	*	–	–	6
Uncontrolled confounding														
Race	–	*	*	*	*	*	*	–	–	*	*	*	*	10
Sex	–	–	–	–	–	–	–	–	–	*	–	–	–	1
Occupation	*	*	*	*	*	*	*	–	–	*	*	*	–	10
Socioeconomic status	*	*	*	*	–	*	*	–	–	*	–	–	–	7
Population density	*	*	*	–	–	*	*	*	*	*	–	*	*	10
Ethnicity	*	*	*	*	*	*	*	–	–	*	*	*	*	11
In/out migration	*	*	*	*	*	*	*	–	–	*	–	–	–	8
Personal habits	*	*	*	*	*	*	*	*	*	*	*	*	*	13
Absence (or incomplete) data on dose-response	*	*	*	*	*	–	–	–	–	–	*	*	*	8
Multiple comparisons problem	*	*	*	*	*	*	*	*	*	–	*	*	*	12
Insensitivity of summary statistics	*	*	*	*	*	–	–	*	*	*	–	*	*	10
Absence of historical asbestos exposure data	*	*	*	*	*	*	*	*	*	*	*	*	*	13
Use of at least one questionable statistical procedure	–	*	–	–	*	–	–	*	*	–	–	–	–	4
Total	14	15	14	12	12	11	11	7	7	11	10	10	9	

[a]Legend: asterisk (*) indicates presence of characteristic; minus (–) indicates absence of characteristic.
[b]In approximate decreasing order of relative impact on definitiveness of study results.

ployed relatively more sophisticated multivariate statistical analyses as an attempt to control for confounding at the group level. Only one study to date, that of Polissar et al. in 1982 (*13*), attempted to collect data on a confounding variable at the individual level; however, since this was done only for cancer cases and not controls, it was not possible to analyze the data on a more sensitive and reliable case-control basis.

Occupation was a particularly important confounding variable in the studies conducted in Quebec (*6,7*), the Bay Area (*8–10*), and Connecticut (*4,5*), since a substantial number of males are employed in the various asbestos-related industries within these areas. The confounding effects of occupation are particularly evident in the two Quebec studies (*6,7*), where positive associations for lung and stomach cancer were consistently confined to males.

Misclassification of asbestos exposures is another serious limitation of all the studies conducted to date. This misclassification results from several factors including: the basic ecologic design, which assigns specific exposures to an entire goegraphic area; tenuous assumptions regarding the extent of asbestos contamination from asbestos pipes; the lack of any reliable historical asbestos exposure data; and the in/out and daily mobility of the study populations.

It is also likely that many of the associations found among the 13 studies are simply chance occurrences arising from the large number of statistical comparisons that were generally made. Whenever a large number of significance tests are performed at a constant significance level, a certain number of tests will be significant by chance alone and the actual significance levels must be higher than those reported by the authors. Among the 13 studies reviewed, the number of separate statistical comparisons reported ranged from 33 to 336 with an average of 193. Therefore, at a 5% level of significance, the number of positive findings expected due to chance alone would range from approximately 2 to 17 with an average across the 13 studies of about 10. In other statistical terms, the probability that at least one of the n independent comparisons was due to chance alone ranged from 0.81 in a study reporting about 30 comparisons to virtual certainty in studies reporting 100 or more comparisons. (At the 5% level of significance, the probability of falsely claiming statistical significance in at least one of n independent comparisons is $1\text{-}0.95^n$.

Objective Integration of Findings

In order to objectively evaluate the extent to which the pattern of findings to date may be due to chance factors, and to better assess the degree of interstudy consistency, a probability analysis was performed for each cancer site, which was examined in at least four independent studies. The studies of Levy et al. in 1976 (*2*), Harrington et al. in 1978 (*4*), Kanerek et al. in 1980 (*8*) and Severson in 1979 (*12*) were not considered independent studies, since they provided no unique information in light of the subsequently updated and improved analyses of Sigurdson et al. in 1981 (*3*), Meigs et al. in 1981 (*5*), Conforti et al. in 1981 (*9*) and Polissar et al. in 1982 (*13*), respectively. In addition, the study of Tarter in 1981 (*10*) was not included in the probability analysis, since no cancer site-specific results were shown.

For each cancer site, the probability analysis consisted of first casting the independent study results of Tables 1 and 2 into a 2 × 2 contingency table of male-female results as shown in Table 5.

The next step in the analysis was to calculate for each cancer site the probability of jointly observing in $n_{..}$ independent studies, $n_{1.}$ or more positive associations in males and $n_{.1}$ or more positive associations in females. This was done assuming that for males and females the probability of observing a positive association in a given independent study due to chance alone is $p = 0.05$, and the probability of observing no association is $(1 - p) = 0.95$. Designating M and F to represent the events of observing a positive association in males and females, respectively, and assuming that outcomes in males and females are independent events, the probability of the joint event (known as a large deviation probability, P_D) can be calculated as the product of two individual cumulative binomial probabilities as follows:

$$P_D = P(M \geq n_{1.}) \cdot P(F \geq n_{.1})$$

$$= \left\{ \sum_{i = n_{1.}}^{n_{..}} \binom{n_{..}}{i} p^i (1 - p)^{n_{..} - i} \right\} \left\{ \sum_{j = n_{.1}}^{n_{..}} \binom{n_{..}}{j} p^j (1 - p)^{n_{..} - j} \right\}$$

P_D was also calculated by using the binomial parameter $p = 0.10$ assuming that a predetermined significance level of $p = 0.05$ would have actually been higher for any individual observed positive association due to the very large number of statistical comparisons that were made in most of the independent studies. Very small values of P_D (less that 0.05, for example) for a given cancer site suggest that the number of observed positive associations in males and females across several independent studies was unlikely to have been generated by chance factors alone, and, therefore, may have a biological basis related to ingested asbestos. The P_D value as calculated above does not, however, take into account the degree of association between male and female findings. Unfortunately, the very small numbers of independent studies showing results for specific cancer sites precluded the calculation of any reliable measure of association. However, in order to provide at least a crude objective comparison of the level of agreement between male and female findings, the well-known phi coefficient given as

$$\phi = (\chi_u^2 / n_{..})^{1/2}$$

was computed where χ_u^2 is the uncorrected chi-square statistic tabulated from the above 2 × 2 contingency table as

$$\chi_u^2 = \frac{n_{..} (n_{11} n_{22} - n_{12} n_{21})^2}{n_{1.} n_{2.} n_{.1} n_{.2}}$$

Values of close to zero indicate little, if any, association, whereas values close to unity indicate almost perfect predictability. By definition, the phi coefficient cannot be determined whenever $n_{1.}$, $n_{.1}$, $n_{2.}$, or $n_{.2}$ is equal to zero. Finally, the strength of the association between male and female findings was assessed through the use of the Fisher-Irwin exact test (*18*).

Table 6 shows the results of the probability analysis for gastrointestinal and nongastrointestinal cancer sites, which were examined in at least four independent studies. Only five of the 14 sites shown in Table 6 (esophagus, stomach, pancreas, lungs, and prostate) are associated with P_D values that range consistently below or near a probability level as low as 0.05, for example. However, as shown by the ϕ value and corresponding Fisher-Irwin probability, or by inspection of the outcome frequencies, the level of agreement between male and female findings for these cancers is generally moderate to low. Specifically, positive associations were jointly observed in males and females in only one of six studies of esophageal cancer, two of eight studies of stomach cancer, and one of eight studies of pancreatic cancer. It was not possible to quantify the level of male-female agreement for lung or several other cancers due to the presence of one or more zero marginal totals.

Two additional neoplasms (small intestine, and leukemia/aleukemia) are associated with P_D val-

Table 5.

		Female association		
		(+)	(0 or −)	Total
Male association	(+)	n_{11}	n_{12}	$n_{1.}$
	(0 or −)	n_{21}	n_{22}	$n_{2.}$
	Total	$n_{.1}$	$n_{.2}$	$n_{..}$

Table 6. Summary of male-female associations in independent studies by cancer site.

Cancer site	No. of independent studies ($n_{..}$)	Outcome (+ +) (n_{11})	(+ 0) (n_{12})	(0 +) (n_{21})	(00) (n_{22})	Total male (+) (n_1)	Total female (+) (n_1)	Large deviation probability (P_D) (p = 0.05)	(p = 0.10)	Index of association ϕ	Fisher-Irwin probability
Gastrointestinal											
Esophagus	6	1	1	0	4	2	1	0.0087	0.0535	0.63	0.33
Stomach	8	2	2	0	4	4	2	<0.0001	0.0009	0.55	0.21
Small intestine	4	1	0	0	3	1	1	0.0344	0.1183	1.00	0.25
Colon	8	0	1	0	7	1	1	0.3366	0.5695	NC[a]	NC
Rectum	8	1	0	0	7	1	1	0.1132	0.3243	1.00	0.12
Biliary passages/liver	4	0	0	0	4	0	0	1.00	1.00	NC	NC
Gallbladder	4	0	0	1	3	0	1	0.1855	0.3439	NC	NC
Pancreas	8	1	1	3	3	2	4	<0.0001	0.0009	0.0	0.78
Peritoneum	4	0	0	1	3	0	1	0.1855	0.3439	NC	NC
Nongastrointestinal											
Bronchus, trachea, lungs	7	0	3	0	4	3	0	0.0038	0.0257	NC	NC
Kidneys	6	0	1	0	5	1	0	0.2649	0.4686	NC	NC
Bladder	5	0	0	0	5	0	0	1.00	1.00	NC	NC
Brain/CNS	5	0	1	0	4	1	0	0.2262	0.4095	NC	NC
Leukemia/aleukemia	6	0	2	0	4	2	0	0.0328	0.1143	NC	NC
Prostate (males only)	4	–	–	–	–	2	–	0.0140	0.0523	–	–

[a]NC = not calculated due to presence of one or more zero marginal frequencies.

ues below 0.05 when based on the binomial parameter p = 2.05, but exceed P_D = 0.05 when based on the more conservative p = 0.10. While still based on very small numbers of independent studies, the P_D values for the remaining cancer sites examined suggest that the number of positive male and female associations, if any, observed for these cancers is more likely to represent chance phenomena.

It should be recognized that, next to very small sample size, the most severe limitation of the above probability analysis was the necessity to assume that the $n_{..}$ independent studies provided qualitatively and quantitatively equivalent information toward the integration of findings for any given cancer site. Therefore, the results of the probability analysis should not be regarded as conclusive, but rather should serve as a rough guide for the future direction and emphasis of research.

Relationship to Occupational Studies

The pattern of integrated findings presented for gastrointestinal cancers is somewhat consistent with patterns observed among workers occupationally exposed to asbestos. Epidemiologic studies of several occupational groups exposed to asbestos have shown an increased incidence of cancer of the esophagus, stomach, colon, and rectum and of peritoneal mesotheliomas (*19–22*). Furthermore, as noted by Mason et al. in 1974 (*1*), certain studies of asbestos installation workers in the United States have shown cancer of the upper gastrointestinal tract to be in far greater excess than cancer of the colon and rectum. This same feature is suggested in Table 6, where upper gastrointestinal cancers are among the strongest positive results, whereas positive associations for colon and rectal cancer are virtually nonexistent. The relatively large number of independent positive associations found for pancreatic cancer suggests a possible link with ingested asbestos, although most occupational studies have not implicated this cancer site.

With respect to nongastrointestinal neoplasms, an increased risk for cancer of the kidneys has been found in a recent occupational study of insulation workers (*23*). A biological basis for this risk has been described by Cook and Olson (*24*). However, as shown in Table 6, kidney cancer was observed in excess among males in only one of the six independent studies reviewed that examined this anatomic site. It is uncertain whether the marginally significant number of leukemia/aleukemia and prostatic cancer findings are related to ingested asbestos, since these are generally not considered in occupational studies as sites where asbestos-induced cancers would occur.

Recommendations for Future Research

Although no individual study or aggregation of studies exists that would establish risk levels from the ingestion of asbestos, the studies to date do provide extremely valuable information that should be carefully considered when developing the protocols of future research.

First, the integrated study findings can be used to generate a rough priority of specific etiologic hypotheses that could be tested in the original settings or in independent study populations via more sensitive and reliable epidemiologic designs. The foremost intensive efforts should be made to further study the relationahip of ingested asbestos to the gastrointestinal neoplasms that displayed the most suggestive findings in the ecologic studies. In approximate order of importance, these would be stomach, pancreas, esophagus, and small intestine. The outcomes of these endeavors could be used to determine whether additional studies of other gastrointestinal neoplasms were warranted. In addition, the integrated findings for prostatic cancer, although less biologically plausible, were sufficiently disconcerting to make the relationship of ingested asbestos to this male neoplasm the subject of another more intensive study.

Second, the existing studies have produced a virtual checklist of methodologic limitations and uncertainties that should be avoided or controlled to the fullest extent possible in all future research efforts. Many of the aforementioned weaknesses and limitations can be avoided by simply choosing more suitable geographic areas for study. The "ideal" study area would be one associated with a long history of a wide range of asbestos exposures of known and well-documented magnitude. This would allow a sufficient latency period for the development of disease and would permit a more sensitive and accurate assessment to be made of dose-response relationships. While none of the areas studied to date can be necessarily considered as ideal, the Bay Area and Puget Sound are relatively the most suitable areas for future research. Further studies in new independent areas should also be considered since this will improve the ability to evaluate the strength and consistency of findings statistically.

Many of the other methodologic limitations are features of the underlying ecologic study designs that were employed. The ability to make a causal inference from ecologic data often can be enhanced using more sophisticated analytical techniques. There will always remain an element of uncertainty, however, until the etiologic hypotheses generated from ecologic studies are tested more definitively at the individual rather than group level.

The diseases implicated in the ecologic studies to date are relatively rare in the general population and are associated with long incubation periods. Thus, the retrospective approach is apropriate using, for example, either an unmatched or matched individual case-control design. Basically, a case-control study would compare the ingested asbestos exposures of individual site-specific cases of cancer (incidence or mortality) with unmatched or matched controls. This approach would enable a much more precise measurement of confounding factors such as occupation, socioeconomic status, tobacco and alcohol consumption, dietary habits, and migration history through personal interviews with each case (or next of kin) and control. While the level of asbestos exposure would probably still be determined by geographic residence, the duration of exposure could be much more accurately measured and controlled by determining length of residence. In addition, individual differences in water ingestion habits due to daily mobility and other personal factors could be assessed during the interviews. It is very important that the case-control protocol include procedures for checking the reliability and validity of the methods used to ascertain historical ingested asbestos exposures.

The number of subjects to be selected for a study of a specific disease-exposure relationship will be a fundamental consideration in planning future studies. Basically, an answer to the question of how many subjects should be selected for a case-control study, for example, depends on the specification of four values: the relative frequency of exposure among controls in the target population p_0; a hypothesized relative risk associated with exposure that would have sufficient biologic or public health importance to warrant its detection R; the desired level of significance α; and the desired study power, $(1 - \beta)$ (*25*). As an illustrative example, Table 7 shows for a standard unmatched case-control design the required sample size n (per group) under the conventional $\alpha = 0.05$ (one-sided), $\beta = 0.20$, and for selected values of R and p_0. In the study areas recommended for individual case-control analysis (the Bay Area and Puget Sound), relative risk levels R for gastrointestinal cancer were generally found by ecologic analysis to be only moderately elevated ($R \simeq 1.1$–2.0), if elevated at all. This is likely to be the case in most areas unless levels of asbestos in the drinking water are inordinately high. In order to detect these putative moderate elevations in relative risk at acceptable statistical error levels (α, β), it will be necessary, as shown in Table 7, to study literally hundreds of cases and controls. This may be a serious drawback when studying the rarer forms of gastrointestinal cancer (e.g., small intestine), for it may be difficult to observe and locate the required number of cases during a reasonable period of time. For some cancers, therefore, it may be necessary to accept somewhat higher levels of statistical errors in order to

Table 7. Unmatched case-control sample sizes needed in each group for $\alpha = 0.05$ (one-sided) and $\beta = 0.20$.

Relative risk R	Proportion of controls exposed, p_0			
	0.25	0.50	0.75	0.90
1.2	1890	1484	2071	4431
1.5	365	303	447	987
1.7	208	179	272	610
2.0	119	107	168	385
2.5	66	63	104	246
3.0	45	45	78	187
5.0	20	24	45	114

test the null hypothesis of no risk with the available number of cases.

In conclusion, there is no question that studies designed at the individual level, such as case-control studies, are now needed to establish firmly risk levels to ingested asbestos. However, as illustrated above, the costs of reliably establishing these risk levels will be high, a fact that should be recognized by the sponsors and investigators of future research in this area.

Funding for this work was provided by the Center for Environmental Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, and the U.S. Environmental Protection Agency, Cincinnati, Ohio, under Cooperative Agreement No. 806815.

The research described in this paper has been peer and administratively reviewed by the U.S. Environmental Protection Agency and approved for presentation and publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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